01-17-02 Petition

PATENT

#16

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re U.S. Patent No.:	5,532,221
Issued:	July 2, 1996
To:	W. James Wang, et al
For:	Ionically Crosslinked Carboxyl-Containing Polysaccharides for Adhesion Prevention
From App. No.:	192,336
Filed:	February 4, 1994

Box Patent Extension
Commissioner for Patents
Washington, D.C. 20231

Docket No.: L15.1-10292

TRANSMITTAL LETTER

1. In regard to the above-identified application, we are submitting the attached:
Three copies of the 10 pg Application For Extension of the Term of U.S. Patent No. 5,532,221 Under 35 U.S.C. 156, plus Exhibits 1-6; Check for $1,120.00; VAS Transmittal Letter and Postcard.

2. With respect to fees:
   - ☐ No additional fee is required.
   - ☒ Attached is check(s) in the amount of $1,120.00
   - ☐ Charge additional fee to our Deposit Account No. 22-0350.

3. **CONDITIONAL PETITION FOR EXTENSION OF TIME**
This conditional petition is being filed along with the papers identified in Item 1 above and provides for the possibility that Applicant has inadvertently overlooked the need for a petition and fee for extension of time or for a petition and fee for any other matter petitionable to the Commissioner as required. If any extension of time for the accompanying response is required or if a petition for any other matter is required, by petitioner, Applicant requests that this be considered a petition therefor.

4. Notwithstanding paragraph 2 above, if any additional fees associated with this communication are required and have not otherwise been paid, including any fee associated with the Conditional Petition for Extension of Time, or any request in the accompanying papers for action which requires a fee as a petition to the Commissioner, please charge the additional fees to Deposit Account No. 22-0350. Please charge any additional fees or credit overpayment associated with this communication to the Deposit Account No. 22-0350.

VIDAS, ARRETT & STEINKRAUS

Date: January 15, 2002 By: _____

Walter J. Steinkraus
Registration No. 29,592

6109 Blue Circle Drive, Suite 2000
Minnetonka, MN 55343-9185
Telephone: (952) 563-3000
Facsimile: (952) 563-3001

Certificate Under 37 CFR 1.8: I hereby certify that this Transmittal Letter and the paper(s) as described herein, are being deposited in the U.S. Postal Service, via EXPRESS MAIL, NO. ET395844396US, addressed to BOX Patent Extension, Commissioner for Patents, P.O. Box 2327, Arlington VA 22202-3513, on January 15, 2002.

Jayne Bisson

Jayne Bisson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re U.S. Patent No.:	5,532,221
Issued:	July 2, 1996
To:	W. James Wang, et al
For:	Ionically Crosslinked Carboxyl-Containing Polysaccharides for Adhesion Prevention
From App. No.:	192,336
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Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

Docket No.: L15.1-10292

Sir:

APPLICATION FOR EXTENSION OF THE TERM OF UNITED STATES PATENT NO. 5,532,221UNDER 35 U.S.C. § 156

Applicant, Lifecore Biomedical, Inc., is a corporation organized under the laws of the State of Minnesota and has a place of business at 3515 Lyman Boulevard, Chaska, Minnesota 55318-3051.

Applicant is the owner of the patent by reason of assignments:

From all inventors to ETHICON INC., recorded in the United States Patent and Trademark Office on **April 12, 1994** at Reel/Frame: **6955/0928**, and

From ETHICON, INC., to LIFECORE BIOMEDICAL, INC. recorded in the United States Patent and Trademark Office on **October 17, 1994** at Reel/Frame: **7170/0589**.

Applicant is the holder of the regulatory market approval for the approved product, GYNECARE INTERGEL Adhesion Prevention Solution. GYNECARE and INTERGEL are registered trademarks of Ethicon, Inc., Applicant's distributor for GYNECARE INTERGEL Adhesion Prevention Solution. The product is also identified in some FDA submissions, and in some of Applicant's commercial literature, as INTERGEL Solution. At the time of initial IDE submission, and for some time thereafter, the product was identified as LUBRICOAT Gel.

Pursuant to the provisions of 37 C.F.R. § 1.710-1.777, Applicant hereby applies for an extension of the term of United States Patent No. 5,532,221 under 35 U.S.C. § 156 based on the materials set forth herein and in Exhibits 1- 6 submitted herewith. The requested extension is for a period expiring on **November 16, 2015**.

The Requirements for a complete application for patent term extension are set forth in 37 C.F.R. § 1.740. Those requirements are reproduced below, immediately followed by the required information, a reference to an accompanying document containing the required information, or a statement of non-applicability.

(a)(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;

GYNECARE INTERGEL Adhesion Prevention Solution is a sterile aqueous solution of ferric hyaluronate and sodium hyaluronate. It is prepared by adding ferric chloride to a solution of sodium hyaluronate. The sodium hyaluronate is prepared by neutralization of the acid groups of powder form hyaluronic acid having an average molecular weight in the range of 500,000 to 1,200,000, using an aqueous alkali neutralizing agent. The hyaluronic acid is obtained as a product of a bacterial fermentation.

GYNECARE INTERGEL Adhesion Prevention Solution is indicated for use in patients undergoing open, conservative gynecologic surgery as an adjunct to good surgical technique to reduce post-surgical Adhesions. GYNECARE INTERGEL Adhesion Prevention Solution is also intended to reduce the likelihood of developing moderate or severe postoperative adnexal adhesions in these patients.

(a)(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred;

GYNECARE INTERGEL Adhesion Prevention Solution was subject to review under the Federal Food, Drug and Cosmetic act, 35 USC §360(e), as a Class III medical device.

(a)(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;

GYNECARE INTERGEL Adhesion Prevention Solution received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred on November 16, 2001. A copy of the approval letter is attached as **Exhibit 1**.

(a)(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

Not Applicable

(a)(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § l.720(f) and an identification of the date of the last day on which the application could be submitted;

This application is being submitted within the sixty day period permitted for submission pursuant to § l.720(f). The last date for on which the application could be submitted is **January 15, 2002.**

(a)(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration;

The names of the inventors are: **W. James Huang, Douglas B. Johns and Richard L. Kroenthal**.

The patent for which an extension is being sought is: **US 5532221**.

The date of issue is: **July 2, 1996**

The date of expiration is: **July 2, 2013**

(a)(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings;

A copy of the patent is attached as **Exhibit 2**.

(a)(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent;

No disclaimer, certificate of correction, or reexamination certificate has issued in the patent.

A copy of the receipt for the first maintenance fee payment is attached as **Exhibit 3**.

(a)(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product,

The patent claims the approved product and a method of using the approved product.

and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product;

Claim 15 reads on the approved product as shown below.

15. An adhesion preventative	GYNECARE INTERGEL Adhesion Prevention Solution is approved for use as an adhesion preventative.
comprising a sterile non-inflammatory hyaluronic acid fraction having a weight average molecular weight of in the range of from about 550,000 to about 8,000,000	GYNECARE INTERGEL Adhesion Prevention Solution includes a sterile non-inflammatory hyaluronic acid fraction. The hyaluronic acid used to prepare the product have a specification for weight average molecular weight of from 500,000 to 1,200,000. The commercial batches to date have all used hyaluronic acid having an average molecular weight above 550,000.
having carboxyl acid groups which are ionically crosslinked by at least one trivalent cation selected from the group consisting of iron, aluminum and chromium	The carboxyl acid groups of the hyaluronic acid are ionically crosslinked with trivalent iron cations.
wherein from about 60 to about 100 percent of the carboxyl acid groups have been ionically crosslinked by said trivalent cations	About 90 percent of the carboxyl acid groups have been ionically crosslinked with the trivalent iron cations.

and the adhesion preventative has a viscosity of at least 2,500 cps.	The viscosity specification for GYNECARE INTERGEL Adhesion Prevention Solution is 3,000 cps to 28,000 cps.

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

Claims 1-6 and 11-14 read on the approved product as shown below.

1. A method of reducing the incidence of post-operative adhesion formation in any animal that is susceptible to unwanted adhesion formation following surgery,	GYNECARE INTERGEL Adhesion Prevention Solution is approved for use in patients undergoing open, conservative gynecologic surgery as an adjunct to good surgical technique to reduce post-surgical adhesions. GYNECARE INTERGEL Adhesion Prevention Solution is also intended to reduce the likelihood of developing moderate or severe postoperative adnexal adhesions in these patients.
comprising the step of topically applying as an adhesion preventative an effective amount of a carboxyl-containing polysaccharide, selected from the group consisting of hyaluronic acid and pharmacologically acceptable salts thereof having a weight average molecular weight of in the range of from about 550,000 to about 8,000,000 which has been ionically crosslinked with a trivalent cation provided in an amount sufficient to crosslink in the range of from about 60 to about 100 percent of the carboxyl groups of the carboxyl-containing polysaccharide, to a site of surgical trauma.	GYNECARE INTERGEL Adhesion Prevention Solution meets the formulation requirements of this step as set forth above with respect to claim 1. It is used by topical application of the solution to a surgical site prior to closure of the site.
2. The method of claim 1 wherein the adhesion preventative is derived from hyaluronic acid, or an alkali or alkaline earth metal salt thereof.	GYNECARE INTERGEL Adhesion Prevention Solution is derived from a sodium hyaluronate solution which is in turn derived from hyaluronic acid.

3. The method of claim 2 wherein the adhesion preventative is derived from hyaluronic acid.	See claim 2 statement.
4. The method of claim 2 wherein the adhesion preventative is derived from sodium hyaluronate.	See claim 2 statement.
5. The method of claim 4 wherein the sodium hyaluronate is ionically crosslinked with a trivalent cation selected from the group consisting of iron, aluminum, and chromium provided in an amount sufficient to crosslink in the range of from about 60 to about 100 percent of the carboxyl groups of the sodium hyaluronate.	The carboxyl groups of the sodium hyaluronate used to prepare GYNECARE INTERGEL Adhesion Prevention Solution are ionically crosslinked with trivalent iron cations. About 90 percent of the carboxyl groups have been ionically crosslinked with the trivalent iron cations.
6. The method of claim 5 wherein the sodium hyaluronate is ionically crosslinked with iron.	See claim 5 statement.
11. The method of claim 1 wherein the adhesion preventative is applied directly to the site of surgical trauma in one application.	GYNECARE INTERGEL Adhesion Prevention Solution is typically applied directly to the site of surgical trauma in one application.
12. The method of claim 11 wherein the adhesion preventative is applied during surgery or at the conclusion of surgery prior to closing.	GYNECARE INTERGEL Adhesion Prevention Solution is typically applied at the conclusion of surgery prior to closing.
13. The method of claim 1 wherein the adhesion preventative is made from hyaluronic acid crosslinked with a trivalent cation selected from the group consisting of iron, aluminum and chromium.	GYNECARE INTERGEL Adhesion Prevention Solution is made from hyaluronic acid crosslinked with trivalent iron cations.
14. The method of claim 13 wherein the viscosity of the adhesion preventative is in the range of from about 2,500 cps to about 250,000 cps.	The viscosity specification for GYNECARE INTERGEL Adhesion Prevention Solution is 3,000 cps to 28,000 cps.

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;

Not Applicable

(a)(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;
(B) The date on which a new drug application (NDA) or a Product License Application (PLA)was initially submitted and the NDA or PLA number; and
(C) The date on which the NDA was approved or the Product License issued;

Not Applicable

(ii) For a patent claiming a new animal drug:

(A) The date a major health or environmental effects test on the drug was initiated, and any available substantiation of that date, or the date of an exemption under subsection (j) of Section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug;
(B) The date on which a new animal drug application (NADA) was initially submitted and the NADA number; and
(C) The date on which the NADA was approved;

Not Applicable

(iii) For a patent claiming a veterinary biological product:

(A) The date the authority to prepare an experimental biological product under the Virus-Serum-Toxin Act became effective;
(B) The date an application for a license was submitted under the Virus-Serum-Toxin Act; and
(C) The date the license issued;

Not Applicable

(iv) For a patent claiming a food or color additive:

(A) The date a major health or environmental effects test on the additive was initiated and any available substantiation of that date;
(B) The date on which a petition for product approval under the Federal Food, Drug and Cosmetic Act was initially submitted and the petition number; and
(C) The date on which the FDA published a Federal Register notice listing the additive for use;

Not Applicable

(v) For a patent claiming a medical device:

(A) The effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device, if no IDE was submitted, and any available substantiation of that date;

(B) The date on which the application for product approval or notice of completion of a product development protocol under Section 515 of the Federal Food, Drug and Cosmetic Act was initially submitted and the number of the application; and
(C) The date on which the application was approved or the protocol declared to be completed;

The required description is provided herewith as **Exhibit 4.**

(a)(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities;

The required description is provided herewith as **Exhibit 5.**

(a)(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined;

The required statement is provided herewith as **Exhibit 6.**

(a)(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see § 1.765);

Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(a)(14) The prescribed fee for receiving and acting upon the application for extension (see § 1.20(j));

The required fee is provided herewith as Check Number 18624. A contingent fee authorization is included in the transmittal to handle any deficiency or overpayment.

and

(a)(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please direct inquiries and correspondence relating to this application for patent term extension to:

Walter J Steinkraus, Reg. No 29592, at the address and phone number associated with **Customer Number 490** (currently 6109 Blue Circle Drive Minnetonka MN 55391, phone 952-563-3000, fax 952-563-3001).

(b) The application under this section must be accompanied by two additional copies of such application(for a total of three copies).

With the exception of the Transmittal Letter, check and postcard receipt, all documents submitted this application are being submitted in triplicate

(c) If an application for extension of patent term is informal under this section, the Office will so notify the applicant. The applicant has two months from the mail date of the notice, or such time as is set in the notice, within which to correct the informality. Unless the notice indicates otherwise, this time period may be extended under the provisions of § 1.136.

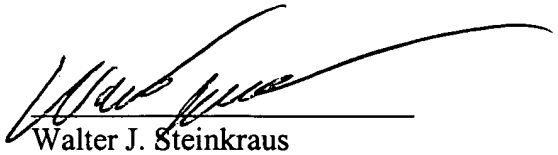
Conclusion

Based on the foregoing, Applicant respectfully submits that the conditions for extension of the patent term set forth in 37 CFR §1.720(a)-(h) have been satisfied and that Applicant is therefore entitled to an extension of the term of United States Patent No. 5,532,221 for a period to expire 14 years from the date of FDA approval, i.e. on November 16, 2015.

The undersigned is a registered practitioner acting on behalf of the Patent owner. (37 CFR §1.730(b)(2)), and is an attorney of record.

Respectfully submitted,
Vidas, Arrett & Steinkraus
Customer Number 490

Dated: January 15, 2002
Suite 2000
6109 Blue Circle Drive
Minnetonka, MN 55343-9131
Phone: (612) 563-3000
Facsimile: (612) 563-3001



Walter J. Steinkraus
Registration No. 29592
Attorney for Applicant

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV 16 2001

James W. Bracke, Ph.D.
President and CEO
Lifecore Biomedical, Inc.
3515 Lyman Boulevard
Chaska, Minnesota 55318-3051

Re: P990015
GYNECARE INTERGEL Adhesion Prevention Solution
Filed: March 8, 1999
Amended: May 12, August 25, September 10, 13, 21 and 29, December 15 and 16, 1999, February 4, April 11, June 2, September 12, 2000, January 5 and November 15, 2001

Dear Dr. Bracke:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the GYNECARE INTERGEL Adhesion Prevention Solution. This device is indicated for use in patients undergoing open, conservative gynecologic surgery as an adjunct to good surgical technique to reduce post-surgical adhesions. GYNECARE INTERGEL Adhesion Prevention Solution is also intended to reduce the likelihood of developing moderate or severe postoperative adnexal adhesions in these patients. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 24 months when the device is stored in refrigerated (2-8°C) or controlled room (15-30°C) temperatures.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for

administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

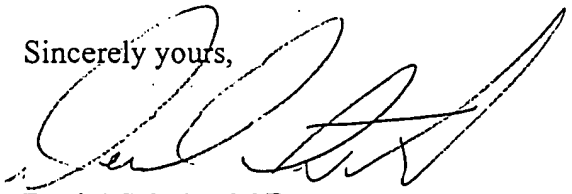
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact David Krause, Ph.D., at (301) 594-3090, ext. 141.

Sincerely yours,



Daniel Schultz, M.D.
Deputy Director for Clinical
and Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 3-4-98, Last modified 8-21-01

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It

allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1)Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a)unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b)reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each

identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1)A mix-up of the device or its labeling with another article.

(2)Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a)has not been addressed by the device's labeling or

(b)has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3)Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of

information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1)May have caused or contributed to a death or serious injury; or

(2)Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers International and Consumer Assistance (DSMICA) at 301-443-8818.

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United States Patent [19]

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[45] Date of Patent: Jul. 2, 1996

[54] **IONICALLY CROSSLINKED CARBOXYL-CONTAINING POLYSACCHARIDES FOR ADHESION PREVENTION**

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[21] Appl. No.: **192,336**

[22] Filed: **Feb. 4, 1994**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 680,955, Apr. 5, 1991, abandoned.

[51] **Int. Cl.**[6] **A61K 31/715**; C07H 13/02

[52] **U.S. Cl.** **514/53**; 514/54; 514/55; 514/56; 514/57; 514/59; 514/60; 514/62; 536/119; 536/121

[58] **Field of Search** 514/53, 54, 55, 514/56, 57, 59, 60, 62; 536/119, 121

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[57] **ABSTRACT**

A method of reducing post-operative adhesion formation by topically applying an ionically crosslinked carboxyl-containing polysaccharide or a pharmacologically acceptable salt thereof, e.g. sodium hyaluronate crosslinked with ferric chloride, to a site of surgical trauma.

15 Claims, No Drawings

IONICALLY CROSSLINKED CARBOXYL-CONTAINING POLYSACCHARIDES FOR ADHESION PREVENTION

BACKGROUND OF THE INVENTION

This is a continuation-in-part of Ser. No. 680,955 filed Apr. 5, 1991, now abandoned, which is hereby incorporated by reference herein.

This invention relates to a method of preventing post-operative adhesion formation. Adhesions are unwanted tissue growth occurring between layers of adjacent bodily tissue or between tissue and internal organs when the healing process begins following a surgical procedure. More specifically, the invention relates to such a method which employs the use of ionically crosslinked carboxyl-containing polysaccharides to control the incidence and extent of adhesion formation at a site of surgical trauma.

The medical and scientific community has extensively studied the therapeutic uses of carboxyl-containing polysaccharides and their water soluble salts for well over a decade. For example, U.S. Pat. No. 4,141,973 (the Balazs patent) discloses the use of a non-inflammatory hyaluronic acid (HA) fraction for numerous therapeutic applications. These applications include, among other things, the prevention of fibrous tissue formation, e.g., the prevention of adhesions; the protection of skin wounds; and the most successful application to date, the use of HA as a viscoelastic ophthalmic during ophthalmic surgery.

The prevention or reduction of adhesion formation following surgery requires a therapeutic agent which has an acceptable half life in bodily tissue. HA, in the free acid form or as its salt (sodium, potassium, etc.), is highly soluble in moist environments. This high solubility as well as susceptibility to naturally occurring enzymes leads to a very short half life of approximately 1 to 3 days in bodily tissue. While this may be acceptable for prevention of adhesions in some indications, for others a longer half life is desirable.

Accordingly, attempts have been made to increase the half life of HA and other carboxyl-containing polysaccharides without sacrificing the therapeutic efficiency of such compounds, particularly for adhesion prevention. For example, U.S. Pat. No. 4,772,419 discloses crosslinking HA with a polyfunctional crosslinking agent which creates ether, ester, or amide linkages. The covalently crosslinked HA forms a gel, and this gel is disclosed as being efficacious for the prevention of adhesions and accretion of tissues. PCT Application WO 89/02445 discloses a water-insoluble derivative of HA prepared by reacting HA with any of a number of different activating agents to prepare a covalently crosslinked HA fraction. PCT Application WO 86/00912 discloses crosslinking HA or other carboxyl-containing polysaccharides with a polyfunctional epoxide to prepare a degradable gel for the prevention of adhesions or accretions of bodily tissue.

Although the attempts to enhance the half life of HA as well as other carboxyl-containing polysaccharides by covalently crosslinking the chosen polysaccharide have met with some success, the biocompatibility and toxicity of the crosslinking agents used for the covalent bonding is unknown. Additionally, the degree of reduction in the incidence of adhesion prevention, although slightly better than HA in its uncrosslinked form, is still inadequate for numerous applications. Therefore, in view of the deficiencies of the prior art, it would be desirable to prepare a derivatized carboxyl-containing polysaccharide which is biocompatible with bodily tissue and exhibits a high degree of adhesion prevention or reduction relative to that of either the native or the covalently crosslinked carboxyl-containing polysaccharides described in the literature.

SUMMARY OF THE INVENTION

The invention is a method of reducing the incidence of post-operative adhesion formation. The invention comprises the step of topically applying as an adhesion preventative an effective amount of an ionically crosslinked carboxyl-containing polysaccharide or a pharmacologically acceptable salt thereof to a site of surgical trauma.

The adhesion preventative in preferred embodiments of this invention has a half life greater than that of the corresponding uncrosslinked polysaccharide, and comparable to that of a corresponding covalently crosslinked polysaccharide. When the adhesion preventative is topically applied to a site of surgical trauma, it exhibits an increased tendency to reduce the incidence of post-operative adhesion formation relative to that of either an uncrosslinked carboxyl-containing polysaccharide or a covalently crosslinked carboxyl-containing polysaccharide. Additionally, the crosslinking agents used for preparing the adhesion preventative are biocompatible and non-toxic to bodily tissue.

The method of this invention can be used in those applications requiring a reduction in the incidence of post-operative adhesion formation, or for any other application which could directly or indirectly benefit from such a therapeutic use, e.g. ophthalmic and orthopedic applications. The ionically crosslinked carboxyl-containing polysaccharide may also be useful as a drug delivery system, e.g. for delivery of wound healing agents, antibiotics, etc.

DETAILED DESCRIPTION OF THE INVENTION

For purposes of defining this invention, a carboxyl-containing polysaccharide is a polysaccharide containing at least one carboxyl group. The polysaccharide chosen may initially contain carboxyl groups or it may be derivatized to contain carboxyl groups. Examples of carboxyl-containing polysaccharides include, but are not limited to, carboxymethyl cellulose, carboxymethyl chitin, carboxymethyl chitosan, carboxymethyl starch, alginic acid, pectin, carboxymethyl dextran, and glucosaminoglycans such as heparin, heparin sulfate, chondroitin sulfate and HA. The most preferred carboxyl-containing polysaccharides are carboxymethyl cellulose, carboxymethyl chitin and HA. The most preferred carboxyl-containing polysaccharide is HA.

The adhesion preventative can employ a carboxyl-containing polysaccharide in the free acid form, or alternatively, a pharmacologically acceptable salt of the polysaccharide can be used. The preferred pharmacologically acceptable salts are alkali or alkaline earth metal salts. Preferably, the adhesion preventative employs the pharmacologically acceptable salt of the carboxyl-containing polysaccharide to prevent the formation of adhesions. Therefore, the most preferred adhesion preventative is sodium hyaluronate.

Carboxyl-containing polysaccharides which can be used to prepare the adhesion preventative are known compounds that are described, for example, in U.S. Pat. No. 4,517,295 and U.S. Pat. No. 4,141,973; and Handbook of Water Soluble Gums and Resins, Chapter 4, by Stelzer & Klug, published by McGraw-Hill, 1980. Processes for preparing the most preferred carboxyl-containing polysaccharide, HA, are illustrated in the Balazs patent, which details a procedure for extracting HA from rooster combs, and in U.S. Pat. No. 4,517,295 which describes a fermentation process for making HA. The HA used to make the adhesion preventative should be highly purified (medical grade quality) for surgical applications.

The crosslinking agents which can be used to ionically crosslink the carboxyl-containing polysaccharide are compounds which possess polyvalent cations, preferably trivalent cations, e.g. ferric chloride, aluminum chloride, chromium sulfate, and aluminum sulfate. The most preferred crosslinking agent is ferric chloride because of its low toxicity and biocompatibility with bodily tissue.

The crosslinking reaction typically occurs almost instantaneously when an aqueous polycation solution is contacted with an aqueous solution of at least 0.5 weight percent of the carboxyl-containing polysaccharide. The concentration of polycationic species present in the reaction mixture should be a concentration sufficient to crosslink at least 10 percent of the carboxyl groups of the polysaccharide. Preferably, the concentration of polycations will be sufficient to crosslink in the range of from about 60 to about 100 percent of the carboxyl groups of the polysaccharide and more preferably in the range of from 70 to 100 percent of the carboxyl groups of the polysaccharide and most preferably in the range of from 80 percent to 95 percent of the carboxyl group of the polysaccharide.

For example, sodium HA is a linear polysaccharide with a disaccharide repeat unit of sodium D-glucuronide and N-acetyl-D-glycocyamine which are linked by beta 1–3 linkages. A concentration of trivalent cation species sufficient to crosslink 60 percent of the carboxyl group would require a concentration of cations sufficient to provide 20 trivalent cations per 100 carboxyl groups. The concentration of trivalent cations per concentration of HA molecules would be dependent on the number of disaccharide repeating units present in each HA molecule. Preferably, the weight average molecular weight of the HA will be in the range of from about 550,000 to about 8,000,000 and most preferably in the range of from about 600,000 to about 2,000,000.

After the reaction, it is usually desirable to adjust pH to about neutral. In some instances, it is necessary to preadjust the polysaccharide solution pH to an acidic pH to prevent precipitation of the HA upon addition of the polycation solution. This often becomes necessary when strong ionic bonds are created, e.g. when the crosslinking agent used is ferric chloride.

An acceptable pH range for HA crosslinked with iron, chromium or aluminum cations is in the range form about pH 4.5 to about pH 8.0. The lower limit was based on sterile I.V. injection saline products which also have a low pH limit of 4.5, while the upper limit was selected to avoid basic pH. Results from preclinical studies indicate that pH within this range has no effect on efficacy. However, based on the pH dependence of gel strength, it is preferred that the pH is in the range of from about 4.5 to about 6. pH higher than 7 might adversely affect long term stability of the gel.

The crosslinking reaction utilizes a polysaccharide possessing anionic groups at each of the carboxyl sites. These anionic groups are ionically bound to the polyvalent cations. The ionically crosslinked polysaccharide, which represents the adhesion preventative used in the method of the invention, is characterized by its tendency to gradually disassociate into its separate ionic species when placed in an ionic medium, e.g. saline.

The viscosity of the adhesion preventative can be controlled by changing the concentration of polysaccharide in solution or by varying the concentration of polycation to control the crosslink density. The adhesion preventative may exist in the form of a gel at relatively high viscosities, or alternately, it may exist as a low viscosity fluid. Generally, the viscosity of crosslinked HA in an aqueous solutions should be at least 2,500 cps measured at room temperature with a Brookfield Model RTVDV-IICP viscometer (using spindle #40 shear rate=3.75 sec^{-1} at 0.5 rpm for viscosities less than 6000 cps or a #52 spindle shear rate=1 sec^{-1} at 0.5 rpm for viscosities greater than 6000 cps). Preferably the viscosity of the crosslinked HA will be in the range of from about 2,500 cps to about 250,000 cps and most preferably in the range of from about 2,500 cps to about 100,000 cps. The viscosity of the crosslinked HA, however, are process-dependent. Longer mixing time or higher shearing rate usually result in lower gel viscosity, although loss due to shear-thinning is reversible at crosslinking densities greater than 50 percent. Regardless of the viscosity which the adhesion preventative exhibits, it may exhibit an increased half life in comparison to an uncrosslinked polysaccharide because of its crosslinked structure.

As used herein, topical application refers to the administration of the adhesion preventative nonsystemically to the surface of the bodily tissue to be treated. The term "site of surgical trauma" is meant to include the site of tissue that has been injured in any way, and includes, for example, tissue sites that have undergone incision, drying, suturing, excision, abrasion, contusion, laceration, anastomosis, manipulation, prosthetic surgery, curettage, orthopedic surgery, neurosurgery, cardiovascular surgery, or plastic or reconstructive surgery. "Site of surgical trauma" also includes tissue that is adjacent to the injured tissue.

The method of this invention can be used to prevent post-operative adhesions in any animal that is susceptible to unwanted adhesion formation following surgery. Advantageously, the method is used to prevent adhesions from developing in mammals, preferably human beings.

The method of the invention is useful in any surgical procedure in which it is desired to inhibit the formation of post-surgical adhesions. It is thus broadly useful in all types of surgery in which adhesion formation can be a complication. For instance, the invention is useful in abdominal surgery, in gynecological surgery, in thoracic surgery, in orthopedic surgery affecting tendons, ligaments, etc., in neurological surgery affecting the dura mater, in liver surgery, and the like.

The adhesion preventative may be administered to the site of surgical trauma by any convenient mode such as, for example, by lavage, by coating directly on the site in a gel, cream, film, or foam, or by any other convenient mode. Preferably, the adhesion preventative is applied directly to the surgical site by injection through a syringe.

The administration of the adhesion preventative can occur at any time before significant wound healing has occurred. It is preferred and most convenient to administer the adhesion preventative during surgery or at the conclusion of the surgical procedure just prior to closing of the wound. However, in some cases, it may be desired to administer the adhesion preventative continually over a period of time.

An "effective amount" of adhesion preventative topically applied to the site of surgical trauma is an amount necessary to affect a reduction in the incidence of post-operative surgical adhesion formation. The amount applied will depend on numerous factors, most significantly of which is the surface area of the site of surgical trauma. Preferably, the amount of preventative applied should be enough to coat the entire area exposed to the surgical trauma, and if necessary or desired, an additional amount sufficient to coat bodily tissue adjacent to those areas actually exposed to the surgical trauma. The effective amount can be readily determined empirically.

The adhesion preventative used to prevent adhesion formation as described in this invention may also be used as a delivery vehicle for other adhesion prevention aids.

For example, the preventative can be used as a delivery vehicle for other well known adhesion preventatives, e.g. tolmetin or other non-steroidal anti-inflammatory drugs (NSAIDS) as described in U.S. Pat. No. 4,937,254, or tissue

plasminogen activator (tPA) as described in European Patent No. 297860. Such a combination may create a synergistic effect between tolmetin and the adhesion preventative to significantly improve the efficacy of either therapeutic agent used alone. Alternatively, the adhesion preventative can be used not only for reducing adhesions but also as a delivery vehicle for other therapeutic agents, such as antibiotics, growth factors and other medicaments.

The following examples are intended to illustrate the claimed invention but are in no way intended to limit its scope.

EXAMPLE 1

Iron-Crosslinked HA Gel with High Crosslink Density as an Adhesion Preventative

(a) Preparation of Gel

0.634 grams of sodium hyaluronate with an average molecular weight of about 600,000 is dissolved in 39.36 g of water for injection in a glass beaker. After a homogeneous aqueous solution is obtained, 1.2 milliliters of a 1 N HCl is added with agitation to adjust solution pH. Then, 5.2 milliliters of a 1.5% ferric chloride solution is added with agitation. Finally, 2.493 ml of a 1.7N NH_4OH solution is added with agitation until a homogeneous gel is obtained with a pH close to neutral. The resulting gel exhibits a viscosity of about 88,600 cps.

(b) Testing Protocol and Efficacy of Adhesion Preventative

Long Evans rats (each weighs about 250 g) are used in this study. Anaesthesia is accomplished with Ketamine (60 mg/Kg) and xylazine (10 mg/Kg) given intraperitoneally. To stimulate adhesions, the cecum is exteriorized and abrasions are made by wiping the cecum with gauze until punctate bleeding develops. Three 8 mm lesions are created on each side of the abdominal wall by removing a layer of the peritoneum and transverse abdominal muscle with a stainless steel biopsy punch. All accessible surfaces of the liver are abraded by rubbing them with the wooden end of a sterile swab. Six rats receive the ferric chloride crosslinked HA gel prepared by the process described in subpart (a) above. Three (3) ml of the ferric HA gel is applied to the cecum, biopsy punch sites and liver at closure of the incision.

Six rats in this study receive no treatment and serve as the control group. Six rats are treated with a lyophilized porous foam of HA covalently crosslinked with Crosslinker CX-100 Polyfunctional Aziridine Crosslinker (from ICI Resins, U.S.). A 6 cm diameter piece of the covalently crosslinked HA foam is cut up into smaller pieces and then placed over the abraded liver areas. Saline is applied to the foam until saturation to hydrate the foam.

Seven days after the surgery, the rats are sacrificed by carbon dioxide inhalation, and the sites are examined for the extent of adhesions. The number of sites and area of cecum adhesions are measured and recorded. The extent of liver adhesions at three sites is graded on a 0-to-6 scale, with a maximum total score of 18 representing the most severe adhesion formation. Ranking of the total scores of the three liver sites is used in statistical analysis of the experimental results. The results are summarized in Table 1.

TABLE 1

Efficacy of Iron Crosslinked HA Gel with High Crosslink Density for Reducing Adhesions

Test Group	Rats with Cecal Adhesions	Avg No. of Adhesion Sites on Cecum	Rats with Liver Adhesions on all Lobes	Avg Total Liver Score (Rank)
Control	5/6	1.67	6/6	11.33 (16.58)
Iron-Crosslinked HA Gel	0/6	0	2/6	2.83 (4.25)***
Covalently-Crosslinked HA Foam*	—	—	2/4**	6.50 (10.13)

*HA foam applied to liver only.
**Two rats died.
***Statistically different from either control or HA foam.

The results indicate that the iron crosslinked HA gel shows significantly lower adhesions to the cecum and between liver lobes relative to the frequency of adhesions exhibited for an untreated control or a covalently crosslinked HA adhesion preventative.

EXAMPLE 2

Iron-Crosslinked HA Gel With Low Crosslink Density as an Adhesion Preventative

The procedure described in Example 1 for preparing the iron crosslinked HA gel, as well as its testing protocol, are substantially repeated to prepare and evaluate an iron crosslinked HA gel with low crosslink density as an adhesion preventative. The following changes are made:

(a) Half of the amount of the ferric chloride solution is used to prepare the iron crosslinked HA gel to reduce the crosslink density, e.g. 2.6 ml of a 1.5% ferric chloride solution is added to the HA solution instead of 5.2 ml of solution which results in a gel of lower viscosity, i.e. 60,200 cps.;

(b) the adhesion preventative is compared with a lyophilized porous foam of HA which is covalently crosslinked with 1,4 butanediol digylcidyl ether instead of Polyfunctional Aziridine Crosslinker; and

(c) the adhesion preventative is additionally compared with non-crosslinked sodium hyaluronate in saline solution exhibiting a viscosity of about 93,800 cps.

The results of the study are shown in Table 2.

TABLE 2

Efficacy of Iron Crosslinked HA Gel with Low Crosslink Density for Reducing Adhesions

Test Group	Rats with Cecal Adhesions	Avg No. of Adhesion Sites on Cecum	Rats with Liver Adhesions on all Lobes	Avg. Total Liver Score (Rank)***
Control	6/6	2.00	6/6	9.50 (A)
Iron-Crosslinked HA Gel	0/6	0	0/6	2.33 (C)
Covalently-Crosslinked Foam*	1/5	0.2	3/5	7.00 (B)
Non-Crosslinked HA**	2/5	0.6	3/5	5.40 (B)

TABLE 2-continued

Efficacy of Iron Crosslinked HA Gel with Low Crosslink Density for Reducing Adhesions

Test Group	Rats with Cecal Adhesions	Avg No. of Adhesion Sites on Cecum	Rats with Liver Adhesions on all Lobes	Avg. Total Liver Score (Rank)***

*Only five rats in this group.
**One rat died.
***Treatment groups with the same letter are not significantly different; the letter designation "C" represents the best statistical results for preventing adhesions.

The results indicate that the iron crosslinked HA gel shows significantly lower adhesions to the cecum and between liver lobes relative to the frequency of adhesions exhibited for an untreated control, a non-crosslinked HA adhesion preventative, or a covalently crosslinked HA adhesion preventative.

EXAMPLE 3

Aluminum-Crosslinked HA Gel as an Adhesion Preventative

(a) Preparation of Gel

1.917 grams of sodium hyaluronate is dissolved in 118.1 grams of water for injection in a glass beaker. After a homogeneous aqueous solution is obtained, 7.2 milliliters of a 5% aluminum chloride hexahydrate solution is added with agitation. Then, 2.2 milliliters of a 1.7N NH_4OH solution is added with agitation until a homogeneous gel is obtained with a pH close to neutral.

(b) Testing Protocol and Efficacy of Adhesion Preventative

Female New Zealand white rabbits of reproductive age (each weighed about 3.0 to 3.5 Kg) underwent uterine horn surgery to induce abdominal adhesion. The procedure involved making a midline incision into the abdomen, traumatizing both uterine horns, applying the crosslinked HA gel, and closing the wound. Twenty (20) rabbits are evenly divided into two groups: the control group, which receives no treatment before closing the wound, and aluminum-crosslinked HA treatment group. For the treated group, 10 milliliters of crosslinked HA gel (prepared according to subpart (a) above) is squirted directly on the uterus wherever adhesions are expected right before closing the wound. Seven days after surgery, each rabbit is sacrificed and a second procedure is performed to evaluate the extent of adhesions. Adhesions are subjectively scored on a scale from 0 (no adhesion) to 4 (severe adhesion) in increments of 0.5 in a blinded randomized manner. Table 3 summarizes the results.

TABLE 3

EFFICACY OF ALUMINUM CROSSLINKED HA GEL FOR REDUCING ADHESIONS

TEST GROUP	NO. OF RABBITS TREATED	MEDIAN SCORE	MEAN RANK
CONTROL	10	3.50	25.0
ALUMINUM CROSSLINKED HA	10	1.00	10.2

TABLE 3-continued

EFFICACY OF ALUMINUM CROSSLINKED HA GEL FOR REDUCING ADHESIONS

TEST GROUP	NO. OF RABBITS TREATED	MEDIAN SCORE	MEAN RANK

The results indicate that the use of an aluminum crosslinked HA gel as an adhesion preventative significantly reduces the incidence of post-operative adhesion formation.

EXAMPLE 4

Tissue Reaction and Half-Life of Iron-Crosslinked HA Gel

Ferric chloride crosslinked HA gel prepared from Example 2 (referred to as the "test" case) and sodium hyaluronate solution (referred to as the "control" case) are injected into the abdominal subcutaneous tissues of rats and analyzed at 1, 3, 7 and 14 days (4 rats/time period) to determine tissue reaction and absorption characteristics. Each animal has 2 test and 2 control 0.5 cc injection sites. Fixation is either by 10% formalin or a pH 7.4 fixative composed of 3% formaldehyde, 0.5% cetylpyridinium chloride and 30 mM NaCl in a 0.1 M phosphate buffer. The latter fixative forms an insoluble complex with glycosaminoglycans (ref: J. Histochem. and Cytochem., 33: 1060–1066, 1985). Hemantoxylin & eosin (H&E) staining is used with selected sites stained with Alcian blue in order to better visualize the HA. Tissue reaction grading is subjective.

Tissue reactions at test and control sites ranged from trace to slight at 1 and 3 days. Neutrophils and macrophages are present at day 1. By day 3 there are predominantly macrophages with smaller numbers of neutrophils and fibroblasts. Frequent macrophages at the day 3 test sites had a fine golden-brown intracytoplasmic pigment. HA is present at the majority of sites at 3 days.

At the day 7 test sites, coarse pigment-containing macrophages are the predominant cell type comprising a minimal to slight tissue reaction. The tissue reactions at the control sites are either zero or trace to minimal and composed predominantly of fibroblasts. There is apparent total absorption of HA at all control sites. A minimal amount of HA is still present at 3/7 test sites.

By 14 days the reactions at test sites are considered to be minimal with a decrease in the overall numbers of pigment-containing macrophages. The majority of control sites are difficult to localize due to a lack of residual tissue reaction. HA has been totally absorbed at all test and control sites by 14 days.

The tissue reactions of both samples are within acceptable limits.

EXAMPLE 5

Pre-clinical Efficacy Evaluation of Crosslinking

Formulae and procedure for preparing the gel at various crosslinking densities are summarized below with an example for making 100 g of a 1% HA (w/w) at 100% crosslinking density.

A. Sources of reagents

Sodium hyaluronate (HA): medical grade, LifeCore Biomedical Inc., molecular weight around 600,000.

Ferric chloride: $FeCl_3.6H_2O$, purified grade, Mallinckrodt, used as bulk pharmaceutical substance, prepared at a concentration of 1.5% (w/w) ferric chloride (not the hexahydrate) in 0.05N HCl before use.

Hydrochloric acid solution: N.F. grade, Mallinckrodt, 10% solution, diluted to 1N before use. Concentration of this solution is checked by pH measurement. A 1N HCL solution should have a pH value of 0.10. However, since most pH-meters tend to give fluctuating readings at this extremely low pH, strength of the solution is checked by measuring the pH of a 10:1 or a 100:1 dilution of the 1N solution, which yields most stable reading (pH=1.06 and 2.02 respectively).

Ammonium hydroxide solution: N.F. grade, Mallinckrodt, 27% NH_4OH solution, diluted to 0.5N before use. Concentration is checked by pH measurement (pH=11.62).

B. Mixing

Step 1: Make an aqueous solution of HA by adding appropriate amount of water.

Example: 1.05 g of HA is mixed with 86.62 g of water under mild stirring (such as a magnetic stirring bar in a beaker for a small scale sample) until homogeneous solution is obtained. This step may take 2 to 24 hours, depending on the type and speed of mixer used, the concentration, and volume of the solution to be made.

Step 2: Add 3.14 ml of 1N HCl to acidity the HA solution. The solution can be easily mixed to homogeneity using the same stirring device in Step 1.

Step 3: Add 4.49 ml of 1.5% ferric chloride. Mixing is done with the same stirrer used in Steps 1 and 2, since viscosity of the acidified HA solution remains low after adding ferric chloride solution.

Step 4: Add 4.70 ml of 0.5N ammonia. Mixing is usually done by an overhead stirrer at a speed between 200 and 700 rpm. The significant increase in viscosity makes mixing much more difficult than in Steps 2 and 3. Mixing conditions might affect gel viscosity.

Step 5: Check pH of the product. Adjustments by adding more ammonia or hydrochloric acid are necessary if pH is not within the desired range. Viscosity should be checked after 8 to 16 hours since it may increase from the viscosity measured immediately after the mixing step, which shear-thins the product.

These formulae are empirical. Whenever possible, a small pilot batch should be made, pH and viscosity checked, before making a larger batch.

C. Apparatus and Methods

Viscosity was measured with a Brookfield Model RVTDV-IICP viscometer at 25° C., 0.5 rpm, unless otherwise specified. Viscosity less than 6,000 cps was measured with spindle #40 (shear rate=3.75 sec^1 at 0.5 rpm), unless otherwise specified. Samples with higher viscosity were measured with spindle #52 (shear rate=1 sec^1 at 0.5 rpm). For samples that exhibited thixotropic behavior, the initial viscosity (before the sample got shear-thinned in the viscometer) was taken as the viscosity of the sample.

Since HA crosslinked with iron (hereinafter, FeHA) viscosity is shear-rate-dependent, it is advisable to use the same spindle throughout, regardless of viscosity level, so that direct comparison between gels can be made. Since the Brookfield Model RVTDV-IICP viscometer yields the lowest shear rate when spindle #52 is used at 0.5 rpm, it is recommended that these two parameters (spindle #52, 0.5 rpm) be kept constant for all measurements in future work to enable consistent comparisons among samples.

pH was measured by either a Corning Model 240 or a Corning Model 250 pH-meter, calibrated with a pH-7 buffer and a pH-4 buffer (from Baxter Scientific Products).

Solutions/gels were prepared by using a Tekmar Type RCT-S19 magnetic stirrer with a stirring bar, or a Heidolph Model RZR-2000 overhead stirrer with various agitators, or a VirTishear homogenizer.

Rabbit Uterine Horn & Rabbit Sidewall Models

Two models, a rabbit uterine horn and a rabbit sidewall model, were utilized in a systematic study to evaluate the two key parameters that may affect the efficacy of FeHA formations, namely crosslinking density and gel viscosity.

Model Description

1) Uterine horn model: The abdomen was exposed through a ventral midline incision. The uterine horns were abraded on each side. Hemostasis was then achieved and a treatment group assigned. Adhesions were assessed by estimating the length of uterine horn with adhesions (maximum 5 cm) at 14±1 days after surgery.

2) Sidewall model: The abdomen was exposed through a ventral midline incision. The cecum was then located and exteriorized. An abrasion was made on the entire cecum by applying digital pressure with gauze (approximately 40 times), until punctate bleeding occurred. The large bowel was then located and abraded. The right sidewall was then exposed. A 3×5 cm lesion was created by scoring the sidewall with a scalpel blade and removing the peritoneum and transverse abdominous muscle. Area (percent) of the sidewall patch with adhesions was recorded at necropsy (7 days post-surgery) along with other parameters.

Tables 4, 5 and 6 summarize completed studies.

TABLE 4

SUMMARY OF STUDIES OF RABBIT SIDEWALL MODEL

FORMULATION	VISCOSITY	pH	ADHESIONS[a] (NORMALIZED)
Control	n/a	n/a	100%
1.2% HA, 0% XL	1,200 cps	7.4	82%
1.7% HA, 0% XL	5,300 cps	6.1	96%
3.0% HA, 0% XL	56,800 cps	6.5	26%
1.2% HA, 1% XL	1,570 cps	6.8	20%
1.2% HA, 5% XL	2,560 cps	5.0	62%
0.9% HA, 25% XL	7,660 cps	7.4	2%
0.68% RA, 50% XL	10,200 cps	5.0	0%
1.5% HA, 50% XL	88,000 cps	4.8	0%
0.45% HA, 90% XL	6,300 cps	6.6	0%
1.0% HA, 90% XL[b]	51,400 cps	4.9	0.1%

[a]defined as % of sidewall adherent in treatment group divided by % of sidewall adherent in control group.
[b]average of two studies

TABLE 5

Summary of Studies of Rabbit Uterine Horn

Treatment	N	Extent (cm) Average	SEM	Percent of Control
Control	6	4.17	0.36	100%
5% XL FeHA	7	4.25	0.31	102%
25% XL FeHA	6	2.04**	0.75	49%

TABLE 5-continued

Summary of Studies of Rabbit Uterine Horn

Treatment	N	Extent (cm) Average	SEM	Percent of Control
50% XL FeHA	7	1.11*	0.43	27%

*p 0.01,
**0.05 (Dunnett's t-test, compared with control)

TABLE 6

Summary of Studies of Rabbit Uterine Horn Model

Formulation	Viscosity	pH	Adhesions[a] (Normalized)
Control	N/A	N/A	100%
1% HA, 0% XL	1,200 cps	7.4	104% (N = 7)
2.75% HA, 0% XL	30,200 cps	5.7	97% (N = 3)
3.65 HA, 0% XL	99,600 cps	6.6	80% (N = 6)
1.2% HA, 5% XL	1,970 cps	5.5	102% (N = 7)
1.0% HA, 25% XL	10,200 cps	7.7	91% (N = 7)
1.0% HA, 50% XL	39,200 cps	5.7	77% (N = 7)
0.9% HA, 25% XL	7,660 cps	7.2	49% (N = 6)
0.68% HA, 50% XL	8,840 cps	7.9	27% (N = 7)
0.45% HA, 90% XL	3,140 cps	5.0	65% (N = 6)
0.68% HA, 90% XL	14,900 cps	4.9	54% (N = 6)
1.0% HA, 90% XL	44,900 cps	7.3	48%[b] (N = 15)
1.43% HA, 90% XL	146,000 cps	5.0	49% (N = 6)

[a]average extent (cm) of treatment group divided by average extent (cm) of control group.
[b]average of two studies.

A clear trend towards improved efficacy with increasing crosslinking density was observed in the rabbit sidewall studies shown in Table 4. Ninety percent crosslinked FeHA virtually eliminated adhesions in the sidewall model. Lower viscosity formulation yield more variable results, though still efficacious in reducing adhesions formation. Among formulations with low viscosities, highly crosslinked FeHA with a lower HA concentration out performed FeHA with a similar viscosity having a lower crosslinking density.

The data in Tables 5 and 6 demonstrates that in the rabbit uterine horn model the efficacy of HA increases with crosslinking density. Table 5 demonstrates that increasing the crosslinking density from 5% to 50% significantly reduces the incidence of adhesions in the rabbit uterine horn model. Table 6 shows a clear trend toward improving efficacy with increasing the crosslinking density from 50% to 90% with similar concentration of HA. Additionally the reproducibility of adhesion prevention is significantly improved at higher crosslinking densities.

What is claimed is:

1. A method of reducing the incidence of post-operative adhesion formation in any animal that is susceptible to unwanted adhesion formation following surgery, comprising the step of topically applying as an adhesion preventative an effective amount of a carboxyl-containing polysaccharide, selected from the group consisting of hyaluronic acid and pharmacologically acceptable salts thereof having a weight average molecular weight of in the range of from about 550,000 to about 8,000,000 which has been ionically crosslinked with a trivalent cation provided in an amount sufficient to crosslink in the range of from about 60 to about 100 percent of the carboxyl groups of the carboxyl-containing polysaccharide, to a site of surgical trauma.

2. The method of claim 1 wherein the adhesion preventative is derived from hyaluronic acid, or an alkali or alkaline earth metal salt thereof.

3. The method of claim 2 wherein the adhesion preventative is derived from hyaluronic acid.

4. The method of claim 2 wherein the adhesion preventative is derived from sodium hyaluronate.

5. The method of claim 4 wherein the sodium hyaluronate is ionically crosslinked with a trivalent cation selected from the group consisting of iron, aluminum, and chromium provided in an amount sufficient to crosslink in the range of from about 60 to about 100 percent of the carboxyl groups of the sodium hyaluronate.

6. The method of claim 5 wherein the sodium hyaluronate is ionically crosslinked with iron.

7. The method of claim 2 wherein the adhesion preventative is administered in combination with another adhesion preventative aid.

8. The method of claim 7 wherein the adhesion prevention aid is a non-steroidal anti-inflammatory drug.

9. The method of claim 8 wherein the non-steroidal anti-inflammatory drug is tolmetin.

10. The method of claim 2 wherein the adhesion preventative is administered in combination with an agent selected from the group consisting of an antibiotic and a growth factor.

11. The method of claim 1 wherein the adhesion preventative is applied directly to the site of surgical trauma in one application.

12. The method of claim 11 wherein the adhesion preventative is applied during surgery or at the conclusion of surgery prior to closing.

13. The method of claim 1 wherein the adhesion preventative is made from hyaluronic acid crosslinked with a trivalent cation selected from the group consisting of iron, aluminum and chromium.

14. The method of claim 13 wherein the viscosity of the adhesion preventative is in the range of from about 2,500 cps to about 250,000 cps.

15. An adhesion preventative comprising a sterile non-inflammatory hyaluronic acid fraction having a weight average molecular weight of in the range of from about 550,000 to about 8,000,000 having carboxyl acid groups which are ionically crosslinked by at least one trivalent cation selected from the group consisting of iron, aluminum and chromium wherein from about 60 to about 100 percent of the carboxyl acid groups have been ionically crosslinked by said trivalent cations and the adhesion preventative has a viscosity of at least 2,500 cps.

* * * * *

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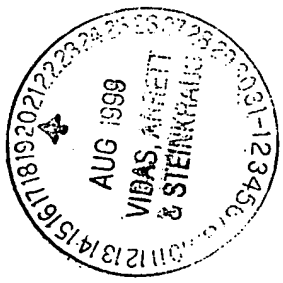
MINNEAPOLIS MN 55343-9131



MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.
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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,532,221	283	470	----	08/192,336	07/02/96	02/04/94	04	YES	PAID

ITM NBR	ATTY DKT NUMBER
1	ETH966

331 91406

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231

GYNECARE INTERGEL Adhesion Prevention Solution
Dates relevant to 35USC§156(g)(3) - Medical Device

(A) Effective Date of IDE: March 17, 1995
IDE no: G950025

(B) Date of Submission of Application for Product Approval
(PMA Filing Date): March 5, 1999
PMA no: P990015

(C) Date of Application Approval: November 16, 2001

INTERGEL Adhesion Prevention Solution REGULATORY CORRESPONDENCE AND SUBMISSIONS

G950025, M980022 and P990015

Date	Description	FDA Supplement /Amendment # (LC #)
2/17/95	LCBI Initial submission for pilot study	0
3/17/95	FDA gives conditional approval for pilot study	
6/1/95	FDA gives full approval for pilot study	
11/17/95	Formal submission requesting expansion to a multicenter study	S007 (4)
12/20/95	FDA contingent approval	
1/15/96	LC revised copy of statistical section	
1/31/96	LCBI responses to contingencies	S008 (5)
3/1/96	FDA approval letter for pivotal study	
3/5/96	Final study report for phase 1 clinical trial	S009
4/4/96	FDA acknowledges final pilot study report. Clinical investigation closed	
6/12/98	LC requests using alternative packaging of clinical supplies and the name of the product changed from LUBRICOAT to INTERGEL. Rev 3 PTL0070	S030
9/16/98	LCBI submits modular PMA plan	
9/28/98	FDA letter assigning # M980022	
10/5/98	LC submits PMA shell with Module M001 (device description)	
10/29/98	LC submits Module 002 (toxicology, biocompatibility and performance standards) for PMA	
11/24/98	LC submits Module 003 (preclinical studies and bibliography)for PMA	
1/12/99	FDA approval & closure of Module 001	
1/29/99	LC submits Module 004 (manufacturing description)for PMA	
3/5/99	LC submits Module 005 (clinical report and labeling). PMA is considered to be filed	
3/8/99	FDA acknowledges the PMA filing and assigns PMA number P990015	

INTERGEL Adhesion Prevention Solution REGULATORY CORRESPONDENCE AND SUBMISSIONS

G950025, M980022 and P990015

Date	Description	FDA Supplement /Amendment # (LC #)
4/26/99	FDA approves filing and grants expedited review	-
5/11/99	LBCI formally submits financial disclosure information and selected tables from the PMA, PTL0013 and PTL0022 protocols	A001
5/21/99	FDA asks questions regarding M004	-
8/22/99	LBCI submits responses to FDA questions of M004	A002
8/25/99	FDA acknowledges receipt of A002	
9/8/99	FDA major deficiency letter	-
9/10/99	LCBI submits responses to minor deficiency questions from the FDA letter of 4/26/99	A004
9/20/99	LCBI submits response to FDA letter of 9/2/99, part 1	A005
9/28/99	LCBI submits response to FDA letter of 9/2/99, past 2	A006
9/29/99	FDA acknowledges receipt of A006	--
10/8/99	LCBI faxes FDA draft panel Pack TOC	--
12/7/99	FDA sends LCBI deficiency letter	--
12/13/99	LCBI submits response to FDA letter dated 12/7/99, Part 1	A007
12/15/99	LCBI submits response to FDA letter dated 12/7/99, Part 2	A008
12/15/99	FDA acknowledges receipt of A007	
1/12/00	FDA panel meeting; panel recommends not to approve product	
2/3/00	LCBI submits letter to J. Dillard re: panel meeting	A009
4/6/00	LC submits letter to C. Witten requesting clarification of areas in dispute	A010
6/2/00	LC files major amendment responding to areas of dispute	A011
9/8/00	LC submits letter to D. Feigal requesting assistance in resolving the dispute	A012
1/4/01	LC submits letter to L. Weinstein requesting the MDDRP	A013

INTERGEL Adhesion Prevention Solution REGULATORY CORRESPONDENCE AND SUBMISSIONS

G950025, M980022 and P990015

Date	Description	FDA Supplement /Amendment # (LC #)
9/6/01	MDDRP held, INTERGEL recommended for unanimous approval	
9/13/01	D. Feigal sends letter stating his agreement with the MDDPR panel recommendation	
11/14/01	LC submits final labeling	A014
11/16/01	FDA sends approval letter	

Updated 1/7/02

GYNECARE INTERGEL Adhesion Prevention Solution

STATEMENT OF ELIGIBILITY

In the Opinion of the Applicant, Lifecore Biomedical, Inc., US patent 553221, whose original expiration period is July 2, 2013, is entitled to an extension of its original term so as to expire on November 16, 2015. The extension term is calculated pursuant to 37 CFR§1.777 as follows (dates are given as MM/DD/YYYY):

37 CFR§1.777(c)

(1) Number of days from beginning of clinical investigation on humans to initial submission of application: 1449

(2) number of days from date of application to approval: 987

Regulatory Review Period 2436

37 CFR§1.777(d)

(1) Subtractions

(i) Number of days in (c)(1) and (c)(2) before patent issue date: 473

(ii) Number of non-diligent days 0

(iii) ½ of [(c)(i) minus [(d)(1)(i) + (d)(1)(ii)] 488

Total subtractions 961

Eligible days 1475

(2) Calculated patent term after adding eligible days to original term of patent: 7/16/2017

(3) Calculated patent term after adding 14 years to date of FDA Approval: 11/16/2015

(4) Earlier of terms calculated under (2) and (3) 11/16/2015

(5)

(i) Calculated patent term after adding 5 years to original expiration date: 7/2/2018

(ii) Earlier of terms calculated under (4) and (5)(i) **11/16/2015**

(6) not applicable

LIFECORE BIOMEDICAL INC

INITIAL SCREENING OF INCOMING PAPERS CHECKLIST

Reviewer: K Chase Date: 1-23-02

APPLICATION NO. 5532221 -36

1. PETITION TYPE CODE

____	R137(a) Petition-------- -501	____	R28c Peition----------309
____	R137(a) Petition ---------509 (Issue Fee/Dwgs)	____	R47 Petition---------- 313
____	R137(b) Petition----------502	____	R53(e) Petition----------408
____	R137(b) Petition----------510 (Issue Fee/Dwgs)	____	R53 (R62 filing date)-----410
____	R137(f) Petition----------536	____	R10 Petition----------411
____	R182 Petition----------519	____	Lost Application----------412
____	R183 Petition----------503	____	R78(a)(3) Petition----------535
____	R378(b) Petition----------532	____	R78(a)(6) Petition----------535
____	R378(c) Petition----------533	____	R55(c) Petition----------535
____	R377 Petition----------521	____	R314 Petition----------508
____	R3.81(b) Petition---------523	____	R55(a) Petition----------507
____	R181 Petition----------515	____	Pet. W/D Abn----------525
____	R181 Petition----------504	____	R705(b)/c-PTA-Bef iss---550
		____	R705(d) PTA-Aft iss-------551
		____	Other_____

2. LIST PAPERS FILED WITH PETITIONS

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3. Is paper a petition to withdraw holding of abandonment: ____yes____no
If so, send paper and/or file to appropriate location ***(Note: remove any flag set first)***:

a. Nonreceipt of action from TC or assertion that reply was timely filed: Send paper to TC_____
b. Nonreceipt of Missing Parts Notice or assertion that reply was timely filed: Send paper to DIRECTOR -OIPE - -CP2-7D25 (PH: 308-0910)
c: Assertion of timely payment of issue fee and/or submission of drawings: Send petition to Office of Publications: ATTN: Tom Hawkins
d. Other_____

4. Other:_____
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